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EXAMINER
ANGELL, JON E

ART UNIT	PAPER NUMBER
1635	16

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Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 07-01)

Office Action Summary	Application No.	Applicant(s)	
	09/888,326	WEINER ET AL.	
	Examiner	Art Unit	
	J. Eric Angell	1635	

-- The MAILING DATE f this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22,24,34,43,56 and 76* is/are pending in the application.

4a) Of the above claim(s) *3,4,22 and 76* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21,24,34,43 and 56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4/13/19
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This Action is in response to the communication filed on 10/15/02, as Paper No. 12.

Claims 1-22, 24, 34, 43, 56, 76 are pending in the application.

Election/Restrictions

2. Applicant's election with traverse of Group I in Paper No. 12 is acknowledged. Applicants arguments regarding the improper restriction of Group I and Group III is considered persuasive.

3. However, this application contains claims directed to the following patentably distinct species of the claimed invention:

i) an immunostimulatory CpG nucleic acid
ii) an immunostimulatory T-rich nucleic acid
iii) an immunostimulatory poly-G nucleic acid

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claims 1, 5-21, 24, 34, 43 and 56 are generic.

Applicant is advised that a reply to this requirement must include an identification of the species that is elected consonant with this requirement, and a listing of all claims readable thereon, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after

the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

4. During a telephone conversation with Alan Steele on December 23, 2002 a provisional election was made without traverse to prosecute: species i) an immunostimulatory CpG nucleic acid. Affirmation of this election must be made by applicant in replying to this Office action. Claims 3, 4, 22 and 76 withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected species or invention.

5. Groups I and III have been rejoined and claims 1, 2, 5-21, 24, 34, 43, and 56, drawn to species i) an immunomodulatory CpG nucleic acid, are addressed herein.

Claim Rejections - 35 USC § 112, second paragraph

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1, 2, 5-21, 24, 43 and 56 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the phrase, "administering… an effective amount to upregulate CD20 expression of a nucleic acid". This phrase renders the claim indefinite because the claim can be interpreted as: 1) upregulating CD20 expression of a nucleic acid (i.e. CD20 expresses a nucleic acid), or 2) upregulating CD20 expression by administering nucleic acid which upregulates CD20 expression. It is unclear how CD20 could express a nucleic acid, therefore the claim (and all depending claims) are indefinite. Appropriate correction is required. For examination purposes, the claim is interpreted as upregulating CD20 expression by administering a nucleic which upregulates CD20 expression

Claim 15 recites the phrase, "wherein the modified backbone is a peptide modified oligonucleotide backbone". This phrase renders the claim indefinite because the claim can be interpreted as: 1) an oligonucleotide backbone comprising a peptide or 2) an oligonucleotide backbone modified by a peptide. It is unclear how a nucleic acid can have a modified backbone comprising a peptide or how a peptide could modify an oligonucleotide backbone. The specification does not define "peptide modified oligonucleotide backbone", but does mention several types of modified backbones including: phosphorothioate, methylphosphonate, methylphosphorothioate, phosphorodithioate, and S- or R- chiral modified backbones (see pages 41-44 of the specification). None of the types of backbone modifications mentioned in the specification appear to be "peptide modified backbones".

Claim 24 recites the phrase, "administering… an effective amount of to induce expression of a surface antigen on a cancer cell surface, of a nucleic acid" (emphasis added). This phrase is unclear and thus renders the claim indefinite. Amending the claim to recite "a

nucleic acid in an amount effective to induce expression of a surface antigen on a cancer cell surface" would obviate this rejection.

Claim 34 recites the phrase, "lower than that of a control B cell". This phrase renders the claim indefinite because the term control B cell is not defined. Amending the claim to recite, "lower than that of a wild-type B cell" would obviate this rejection.

Claim 43 recites the phrase, "an antibody specific for the antigen to which the lymphoma is resistant". This phrase renders the claim indefinite because the claim can be interpreted as: 1) the lymphoma is resistant to a surface antigen; or 2) the lymphoma is resistant to an antibody specific for a surface antigen. It is unclear how a lymphoma would be resistant to a surface antigen.

Claim 56 recites the limitation "the cancer cell" in line 4. There is insufficient antecedent basis for this limitation in the claim.

Additionally, method claims require an active or positive step that accomplishes the goals for the method which were stated in the method's preamble. Claims 1, 24, 34 and 43 lack such a step and are confusing because the additional method step(s) is not sufficiently set forth. While minute details are not required in method claims, at least the basic steps must be recited in a positive, active fashion. See Ex parte Erlich, 3 USPQ2d1011, p.1011 (Bd. Pat. App. Int. 1986). The specific problem with the instant claims is that the steps presented are simply a method of treating or preventing cancer. There is no requirement or active or positive step in the claims that the cancer is treated or prevented. This is indefinite because it leaves the scope of the claim unclear as to whether it is required that the cancer is actually treated or prevented.

Claim Rejections - 35 USC § 112, first paragraph

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claim 24 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Written Description Guidelines for examination of patent applications indicates, "the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, or by disclosure of relevant, identifying characteristics, i.e. structure or other physical and/or other chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show applicant was in possession of the claimed genus." (See MPEP 2164).

In the instant case the claim encompasses administration of any nucleic acid which induces the expression of any cancer antigen (i.e. surface antigen) in a any type of cancer cell. Therefore, the claims encompass a genus of possibly millions of different nucleic acids considering every possible nucleic acid which could stimulate the expression of any cancer antigen expression

(including unknown antigens) in any type of cancer cell. The specification indicates one sub-genus of immunostimulatory nucleic acids which comprise an unmethylated CpG motif and are known to induce the expression of certain cancer antigens in lymphoma cells (including CD20, CD40, CD54, CD69, CD80, CD86, surface Ig, etc.), thus indicating distinct structural and functional properties of one sub-genus of molecules embraced by the claim. However, as mentioned above, the claim encompasses any nucleic acid molecule which induces expression of any cancer antigen in any cancer cell. Therefore, the claim encompasses a number of sub-genuses of nucleic acids such as antisense oligonucleotides and phosphorothioate modified oligonucleotides which do not comprise unmethylated CpG motifs as well as nucleic acid molecules which encoded polypeptides that, when expressed, induce expression of the antigen(s). There is no disclosure in the specification or prior art indicating by example or indicating a correlation between the structure and function of any other genus of nucleic acid which would induce the expression of any cancer antigen. Furthermore, the claim encompasses inducing the expression of any cancer antigen (including new antigens that have not been identified) in any type of cancer cell. There is no written description for any species of nucleic acid molecule which would induce the expression of any unknown cancer antigen in any cancer cell. It is impossible to predict which nucleic acid molecules would be effective at inducing any unknown cancer antigen in any cancer cell. Therefore, the claim encompass nucleic acid molecules which are not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

10. Claim 24 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claim encompasses administration of any nucleic acid which induces the expression of any cancer antigen in a any type of cancer cell. As mentioned in the written description rejection above, the claim encompasses nucleic acid molecules which are not described in the specification. Furthermore there is no description of the nucleic acid molecules which would induce the expression any unknown cancer antigen in any cancer cell. Therefore, additional experimentation is required in order for one of skill in the art to be able to make and use the invention with a reasonable expectation of success. In order to make and use the claimed invention, a number of nucleic acids that induce expression of any cancer antigen in any type of cancer that would be representative of all nucleic acids encompassed by the claims would have to be identified. Regarding the description of a representative number of species, the written description guidelines note, "a satisfactory disclosure of a 'representative number' depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (Emphasis added; see: Federal Register: December 21, 1999, Volume 64, Number 244; revised guidelines for written description). In the instant case, no common attributes or features are disclosed. There is no indication of any relevant common structural/chemical characteristics, and no identification of any structural limitations/requirements which provide guidance on the identification of molecules that meet the functional limitations. Identification of the necessary attributes/features common to all nucleic

acids encompassed by the claim is required. This would require a tremendous amount of experimentation which would take years to complete. Therefore, it is concluded that an undue amount of additional experimentation is required for one of skill in the art to be able make and use the broadly claimed invention.

11. Claim 34 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Written Description Guidelines for examination of patent applications indicates, "the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, or by disclosure of relevant, identifying characteristics, i.e. structure or other physical and/or other chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show applicant was in possession of the claimed genus." (See MPEP 2164).

In the instant case the claim encompasses first identifying any surface antigen that is not on the surface of or is present at a lower level than in a B-cell lymphoma cell compared to a control B-cell, and then administering an antibody specific for said antigen and a nucleic acid which upregulates the expression of said antigen on the surface of a the B-cell. Therefore, the claims encompass a genus of possibly millions of different molecules first considering every possible surface antigen that is present at low levels or not present at all on a B-cell lymphoma

cell but which is present on a control B-cell (which most likely includes currently unidentified antigens); and second considering every possible nucleotide which would stimulate expression of said antigen in said B-cells.

The specification indicates one species of immunostimulatory nucleic acid comprising an unmethylated CpG motif which is known to induce the expression of certain cancer antigens in lymphoma cells. However, there is no disclosure in the specification or the art which indicates that the disclosed species of immunostimulatory nucleic acid would stimulate expression of every possible B-cell cancer antigen, in particular there is no indication that the immunostimulatory nucleic acids disclosed will be capable of upregulating the expression of any unidentified antigens. It is impossible to predict which nucleic acid molecules would be effective at upregulating expression of any unknown cancer antigens in a malignant B-cell. Therefore, the claim encompass antigens and nucleic acid molecules which are not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

12. Claim 34 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claim encompasses first identifying any surface antigen that is not on the surface of, or is present at a lower level than in a B-cell lymphoma cell compared to a control B-cell, then treating the B-cell lymphoma by administering an antibody specific for said antigen and a nucleic acid which upregulates the expression of said antigen on the surface of a B-cell cancer

cell. As mentioned in the written description rejection above, the claim encompasses antigens and nucleic acid molecules which are not described in the specification. Furthermore there is no description of the antigens or the nucleic acid molecules which would induce the expression of the cancer antigen in a B-cell lymphoma. Therefore, additional experimentation is required in order for one of skill in the art to be able to make and use the invention with a reasonable expectation of success. In order to make and use the claimed invention, a number of antigens which would be representative of every B-cell lymphoma antigen would have to be identified. Regarding the description of a representative number of species, the written description guidelines note, "a satisfactory disclosure of a 'representative number' depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (Emphasis added; see: Federal Register: December 21, 1999, Volume 64, Number 244; revised guidelines for written description). In the instant case, no common attributes or features are disclosed. There is no indication of any relevant common structural/chemical characteristics, and no identification of any structural limitations/requirements which provide guidance on the identification of molecules that meet the functional limitations. Identification of the necessary attributes/features common to the B-cell lymphoma surface antigens and nucleic acid molecules which upregulate their expression is required. This would require a tremendous amount of experimentation. Therefore, it is concluded that an undue amount of additional experimentation is required for one of skill in the art to be able make and use the broadly claimed invention.

13. Claim 43 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Written Description Guidelines for examination of patent applications indicates, "the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, or by disclosure of relevant, identifying characteristics, i.e. structure or other physical and/or other chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show applicant was in possession of the claimed genus." (See MPEP 2164).

In the instant case the claim encompasses treating a lymphoma that is resistant to antibody therapy by administering an antibody specific for a surface antigen on said lymphoma and a nucleic acid which upregulates the expression of said surface antigen on said lymphoma cell surface. Therefore, the claims encompass a genus of possibly millions of different molecules considering 1) every possible lymphoma resistant to antibody treatment (including all possible unidentified lymphomas resistant to antibody treatment); 2) every possible surface antigen encompassed by the claim (including all possible unidentified antigens); and 3) every possible nucleotide which could stimulate expression of said surface antigen(s).

The specification indicates one species of immunostimulatory nucleic acid comprising an unmethylated CpG motif which is known to induce the expression of certain cancer antigens in lymphoma cells. However, there is no disclosure in the specification or in the art which indicates

that the disclosed species would upregulate expression of every possible antigen in a lymphoma cell that is resistant to antibody treatment. In particular there is no indication that the described species would be capable of upregulating the expression of any unidentified antigens. It is impossible to predict which nucleic acid molecules would be effective at upregulating expression of any unknown antigens in a lymphoma cell resistant to antibody therapy. Therefore, the claim encompass antigens and nucleic acid molecules which are not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

14. Claim 43 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claim encompasses treating a lymphoma that is resistant to antibody therapy by administering an antibody specific for a surface antigen on said lymphoma and a nucleic acid which upregulates the expression of said surface antigen on said lymphoma cell surface. As mentioned in the written description rejection above, the claim encompasses antigens and nucleic acid molecules which are not described in the specification. Furthermore there is no description of the antigens or the nucleic acid molecules which would induce the expression of the cancer antigen in a lymphoma cell resistant to antibody therapy. Therefore, additional experimentation is required in order for one of skill in the art to be able to make and use the invention with a reasonable expectation of success. In order to make and use the claimed invention, a number of antigens and nucleic acid molecules which would be representative of all species of antigens and

nucleic acids would have to be identified. Regarding the description of a representative number of species, the written description guidelines note, "a satisfactory disclosure of a 'representative number' depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (Emphasis added; see: Federal Register: December 21, 1999, Volume 64, Number 244; revised guidelines for written description). In the instant case, no common attributes or features are disclosed. There is no indication of any relevant common structural/chemical characteristics, and no identification of any structural limitations/requirements which provide guidance on the identification of molecules that meet the functional limitations. Identification of the necessary attributes/features common to all antigens and nucleic acids encompassed by the claim is required. This would require a tremendous amount of experimentation. Therefore, it is concluded that an undue amount of additional experimentation is required for one of skill in the art to be able make and use the broadly claimed invention.

15. Claim 56 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The written description guidelines are mentioned above.

In the instant case the claim encompasses treating any human cancer by administering an immunostimulatory nucleic acid and an IgG1 antibody which binds to a cell surface antigen of a

cancer cell. Therefore, the claim encompasses antibodies for cell surface antigens that have not been identified (i.e. unknown antigens). The claims encompass a genus of possibly millions of different molecules considering every possible antigen encompassed by the claim (including all unidentified antigens of all human cancers) and further considering all of the IgG1 antibodies specific for the antigens.

The specification indicates a number of cell surface antigens which are expressed on the surface of certain human cancer cells such as: CD20, CD40, CD22, CD19, etc. However, there is no disclosure indicating any common attributes or structural elements which are common to all surface antigens on all cancer cells. Therefore, the claim encompasses antigens and antibodies which are not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

16. Claim 56 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claim encompasses treating any human cancer by administering an immunostimulatory nucleic acid and an IgG1 antibody which binds to a cell surface antigen of a cancer cell. Therefore, the claim encompasses antibodies for cell surface antigens that have not been identified (i.e. unknown antigens). As mentioned in the written description rejection above, the claim encompasses antigens and antibodies which are not described in the specification. Therefore, additional experimentation is required in order for one of skill in the art to be able to

make and use the invention with a reasonable expectation of success. In order to make and use the claimed invention, a number of antigens which would be representative of every possible antigen on every human cancer would have to be identified. Regarding the description of a representative number of species, the written description guidelines note, "a satisfactory disclosure of a 'representative number' depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (Emphasis added; see: Federal Register: December 21, 1999, Volume 64, Number 244; revised guidelines for written description). In the instant case, no common attributes or features are disclosed. There is no indication of any relevant common structural/chemical characteristics, and no identification of any structural limitations/requirements which provide guidance on the identification of molecules that meet the functional limitations. Identification of the necessary attributes/features common to all cancer surface antigens is required.

Although the production of antibodies themselves does not require undue experimentation, the production of antibodies for unknown antigens does require a large amount of additional experimentation considering the amount of work required to identify the unknown antigens. Therefore, it is concluded that an undue amount of additional experimentation is required for one of skill in the art to be able make and use the broadly claimed invention.

17. Claims 1, 2 and 5-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A method for inhibiting B-cell lymphoma tumor growth comprising administering to a subject having a B-cell lymphoma tumor:

a) an immunostimulatory nucleic acid sequence that is 6 or more nucleotides in length and comprises an unmethylated CpG motif and further comprises a phosphorothioate modified backbone, wherein said immunostimulatory CpG nucleic acid is administered in an amount effective to upregulate CD20 expression in said B-cell lymphoma; and

b) an anti-CD20 antibody;

wherein administration of the immunostimulatory CpG nucleic acid and anti-CD20 antibody results in the inhibition of B-cell lymphoma tumor growth;

does not reasonably provide enablement for all embodiments embraced by the claim. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,
"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention:

The instant claims are drawn to a method of treating or preventing cancer by

administering: a) a nucleic acid in an amount effective to upregulate CD20 expression and b) and

anti-CD20 antibody. Therefore the general nature of the invention is cancer therapy and encompasses a administrating a combination of an anti-CD20 antibody and a nucleic acid.

The breadth of the claims:

The breadth of the claims is very broad. For instance the claims encompass treating or preventing any kind of cancer by administering any nucleic acid which upregulates CD20 expression (including a nucleic acid which encodes and expresses an CD20, as well as oligonucleotides which induce anti-CD20 expression) and an anti-CD20 antibody.

The unpredictability of the art and the state of the prior art:

It is noted that the claim encompasses administering any nucleic acid which upregulates CD20 expression, thus the claim embraces administering a nucleic acid encoding CD20 or a factor which induces expression of CD20. Therapeutic administration of a nucleic acid encoding and expressing a polypeptide is a method of gene therapy.

At the time of filing, the relevant art considered gene therapy as a whole to be unpredictable as modes of delivery that would provide efficient expression of genes encoding the therapeutic polypeptide sufficient to provide an alleviation of symptoms related to the target disease or condition had not been developed. Currently, the state of the art of gene therapy is still in its infancy as the art is plagued by unpredictability. For instance, Crystal (Science, 1995; 270:404-409) teaches, "All of the human gene transfer studies have been plagued by inconsistent results, the basis of which are unclear" (see page 409, first col.), and sites specific examples including inconsistent results, the inconsistency of results in animal models and humans, vector production problems, and vector efficiency (see page 409, columns 1-2). Specifically, regarding the ideal gene therapy vector, Crystal teaches, "The vector should be specific for its target, not

recognized by the immune system, stable and easy to reproduce… Finally it would express the gene (or genes) it requires for as long as long as required in an appropriately regulated fashion." (See p. 409, second column).

More recently, Walther and Stein (2000) indicate, "The majority of clinical trials using viral vectors for gene therapy in humans still lack a significant clinical success, defining the still existing barriers to achieving clinical benefits with gene therapy" (See pg.267, Discussion section). Walther and Stein also indicate, "The majority of clinical trials using viral vectors for gene therapy in humans still lack a significant clinical success, defining the still existing barriers to achieving clinical benefits with gene therapy" (See pg.267, Discussion section).

Regarding the unpredictable nature of cancer gene therapy, Greco et al. (Front. Biosci. Vol. 7:d1516-24; 2002) teaches,

> "Some major problems remain to be solved before this strategy becomes routinely adopted in the clinic, one of the main challenges being the improvement of gene delivery. Namely, the development of DNA vectors characterized by maximum efficiency and minimal toxicity will define the success of gene therapy and its chances of being accepted by public and clinicians. A number of issues need to be considered. The "magic" vector should be targeted, protected from degradation and immune attack, and safe for the recipient and the environment. Moreover, it should express the therapeutic gene for as long as required, in an appropriately regulated fashion." (see p. d1516, abstract).

Regarding the use immunostimulatory nucleic acids, the art recognizes a number of specific characteristics of the oligonucleotide which are critical for its function as an immunostimulatory molecule. For instance, Krieg (BioDrugs, 1998; 5:341-346) teaches,

> "Synthetic oligonucleotides ranging in length from 8 to 30 nucleotides or more could cause immune stimulation if there was only a single CpG dinucleotide as long as this was not preceded by a C or followed by a G. Most importantly, the CpG dinucleotide had to be unmethylated: if the C was replaced by 5-methyl-cytosine, then the oligonucleotide lost its immune stimulatory activity." (See p. 342, first paragraph).

Similarly, Agrawal et al. (Trends in Mol. Med., 2002; 8:114-121) teaches, "The presence of unmethylated CpG dinucleotide is essential for the induction of immunostimulatory activity..." (See p. 114, bottom of second column). Agrawal also teaches that sequences required for CpG related immune stimulation varies from species to species, and indicates, "The optimal motif for recognition by human immune cells is GTCGTT or TTCGTT" (See p. 115, first paragraph). Thus indicating that an oligonucleotide of 6 nucleotides in length can function as an immunostimulatory agent in humans.

Hartmann et al. (J. Immunology, 2000; 164:1617-1624) teaches that the oligonucleotide must be protected from nuclease degradation in order to be effective in vivo. Specifically, Hartmann teaches, "To have in vivo clinical utility, ODN must be administered in a form that protects them against nuclease degradation. The native phosphodiester internucleotide linkage can be modified to become highly nuclease resistant via replacement of one of the nonbridging oxygen atoms with a sulfur, which constitutes phosphorothioate ODN." (see p. 1618, first column).

Therefore, in order for an oligonucleotide to stimulate an immune response in vivo it must contain an unmethylated CpG motif, be at least 6 nucleotides in length, and be protected from nuclease degradation by comprising, for example, modified backbone linkage, such as a phosphorothioate linkage.

There is no teaching in the prior or post-filing art indicating that any cancer can be prevented, thus indicating the high degree of unpredictability of preventing cancer. In fact, methods for preventing cancer would encompass all of the problems associated with treating

cancer, as well as additional obstacles such as preventing the events that lead to transformation of a normal cell into a cancer cell including preventing genetic mutation, and immortalization.

Working Examples and Guidance in the Specification

The specification has one working example specifically indicating that when mice comprising a B-cell lymphoma (T3C cells), were administered CpG ODN 1826 (a 20mer oligonucleotide with a phosphorothioate backbone (SEQ ID NO: 560) and a mouse IgG2a monoclonal antibody (MS11G6), the mice had a significantly improved survival when compared to control mice (see Example 3, pages 76-77), thus indicating that the treatment inhibited growth of the B-cell lymphoma. The specification also provides guidance on constructing an immunostimulatory oligonucleotide comprising at least one umethylated CpG dinucleotide. The specification also indicates a general formula for the immunostimulatory oligonucleotide. It is disclosed that the CpG nucleic acid is represented by at least the formula (emphasis added):

5' $N_1X_1CGX_2N_2$ 3'

wherein X_1 and X_2 are nucleotides and N is any nucleotide and N_1 and N_2 are nucleic sequences composed of from about 0-25 N's each (see p. 38 of the specification).

It is noted that there are no examples or guidance indicating anything other than an immunostimulatory nucleic acid comprising an unmethylated CpG motif can be used to upregulate CD20 expression. Also, there are no examples or guidance disclosing the method as useful for treating any kind of cancer other than a B-cell lymphoma, and there is no example/guidance indicating that cancer was prevented.

Quantity of Experimentation

Considering the breadth of the claims and the limited working examples and guidance in the specification, one of skill in the art would be required to perform additional experimentation in order to be able to effectively use the invention to the full scope of the claims with a reasonable expectation of success. For instance, there is no indication in the specification or prior art that a nucleic acid encoding an tumor antigen (such as CD20) could be effectively delivered to any cancer in vivo in such a way that resulted in the proper expression of the antigen and proper display of the antigen on the surface of the cancer cell at a concentration high enough, and for a long enough duration of time in order to effectively treatment or prevent any cancer. Considering the teaching in the art and the examples and guidance in the specification, one of skill in the art could use the method for inhibiting growth of a B-lymphoma tumor provided the nucleic acid comprises an oligonucleotide comprising at least one unmethylated CpG motif, at least 6 nucleotides in length, and has a phosphorothioate modified backbone. However, additional experimentation would be required in order to use any nucleic acid that does not specifically have these characteristics to treat or prevent any type of cancer. For instance, one would have to show how a nucleic acid comprising only methylated CpG motifs could function as immunostimulatory molecules, considering the teaching in the art that it is imperative to have at least one unmethylated CpG motif. Also, additional experimentation would have to be done in order to overcome the teaching in the art that the ODNs must be administered in a form that protects them from nuclease degradation and that the nucleic acid must be at least 6 nucleotides in length in order to be effective. The amount of additional experimentation is deemed to be undue because in order to practice the full scope of the claimed invention with a reasonable expectation of success, one of skill in the art would have to show evidence overcoming art

recognized problems that the broad method would not work for treating or preventing any cancer.

Level of the skill in the art

The level of the skill in the art is deemed to be high.

Conclusion

Considering 1) the high degree of unpredictability of recognized in the art, particularly the problems associate with gene therapy and the required characteristics of the nucleic acid in order to be an effective in vivo immunostimulatory nucleic acid sequence; 2) the breadth of the claims as mentioned above; 3) the limited number of working examples and guidance in the specification; and 4) the high degree of skill required, it is concluded that the amount of experimentation required to perform the broadly claimed method is undue.

Claim Rejections - 35 USC § 102

18. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

19. Claims 1, 2, 5, 7, 13, 14, 16-19 and 21 rejected under 35 U.S.C. 102(b) as being anticipated by Wooldridge et al. (Blood, 1997; 89:2994-2998).

Wooldridge teaches a method of inhibiting B-cell lymphoma growth wherein an isolated synthetic immunostimulatory oligonucleotide 18 nucleotides long comprising a phosphorothioate modified backbone and an unmethylated CpG motif (see p. 2995, first column and Figure 1) was administered (300ug) to mice comprising a B-cell lymphoma. Specifically, the tumor cells are 38C13 cells (p. 2995, bottom of first column), which are known to be associated with a low level of CD20 expression. The oligonucleotide treatment is followed by administration of a mouse IgG2a monoclonal antibody. Specifically, the antibody is MS11G6, an anti-CD20 antibody (see p. 2994, last paragraph, the same antibody used in Example 3 of the specification p. 76-77). It is noted that although Wooldridge does not specifically indicate that the oligonucleotide administration results in the upregulation of CD20 expression, Wooldridge does teach administration of 300ug of the oligonucleotide, which is clearly in the dose range disclosed in the specification (see p. 63 lines 10-15 of the specification, which indicates, "doses of the compounds disclosed herein typically range from about 0.1ug to 10mg per administration"). Therefore, administering the oligonucleotide using the method taught by Wooldridge would necessarily upregulate the expression of CD20 because the effective dose taught by Wooldridge is within the range of efficacy contemplated in the specification (see p. 63, lines 10-15 of the specification).

20. Claims 1, 2, 5, 7, 12-14 and 16-21 are rejected under 35 U.S.C. 102(a) as being anticipated by Warren et al. (Clin. Lymphoma, June 2000; 1:57-61, IDS reference C159).

Warren teaches that bacterial DNA or synthetic oligonucleotides containing unmethylated CpG motifs can be immunostimulatory molecules (see p. 57, abstract). Warren

teaches a method of inhibiting B-cell lymphoma growth wherein a synthetic immunostimulatory oligonucleotide 20 nucleotides long comprising a phosphorothioate modified backbone and an unmethylated CpG motif and which was not known to hybridize with genomic DNA or RNA under stringent conditions (see p. 57, last paragraph and p. 58, first paragraph) can be administered (2-200ug) to mice comprising a B-cell lymphoma (see p. 58, second paragraph). Specifically, the tumor cells are 38C13 cells (p. 57, last paragraph), which are known to be associated with a low level of CD20 expression. The treatment includes administration of the oligonucleotide and a mouse IgG2a monoclonal antibody. Specifically, the antibody is MS11G6, an anti-CD20 antibody (see p. 57, last paragraph; the same antibody used in Example 3 of the specification p. 76-77). Warren teaches that the administration of the antibody can be prior to, simultaneous with, or after administration of the oligonucleotide (see p. 59, Table I). It is noted that although Warren does not specifically indicate that the oligonucleotide administration results in the upregulation of CD20 expression, Warren does teach administration of 2-200ug of the oligonucleotide, which is clearly in the dose range disclosed in the specification (see p. 63 lines 10-15 of the specification, which indicates, "doses of the compounds disclosed herein typically range from about 0.1ug to 10mg per administration"). Therefore, administering the oligonucleotide using the method taught by Warren would necessarily upregulate the expression of CD20 because the effective dose taught by Warren is within the range of efficacy contemplated in the specification (see p. 63, lines 10-15 of the specification).

Claim Rejections - 35 USC § 103

21. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

22. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

23. Claims 5, 6, 8-12 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wooldridge et al. (Blood, 1997; 89:2994-2998) in view of Krieg et al. (BioDrugs, 1998; 10:341-346.

Wooldridge teaches a method of inhibiting B-cell lymphoma growth wherein an immunostimulatory oligonucleotide 18 nucleotides long comprising a phosphorothioate modified backbone and an unmethylated CpG motif (see p. 2995, first column and Figure 1) was administered (300ug, an amount which would necessarily upregulate CD20 expression as mentioned above) to mice comprising a B-cell lymphoma. The oligonucleotide treatment was followed by administration of a mouse IgG2a monoclonal antibody specific for CD20.

Wooldridge does not specifically teach: 1) the immunostimulatory nucleic acid is bacterial DNA or eukaryotic DNA; 2) the type B-cell lymphoma that is treated is a B-CLL or a marginal zone lymphoma; 3) the CD20 antibody used is specifically C28B or Rituximab; 4) the nucleic acid used would not hybridize with genomic DNA or RNA under stringent conditions; or 5) that the oligonucleotide and antibody can be administered together.

However, considering that Wooldridge recognizes that bacterial DNA and synthetic DNA comprising unmethylated CpG motifs are effective immunostimulatory molecules (see p. 2994, abstract and first column), and also considering that the art recognizes that unmethylated CpG sequences (as long as it is not preceded by a C or followed by a G) can stimulate an immune response, regardless of the source of the nucleic acid (e.g. see Krieg p. 346 and 347, first paragraph) and also considering there is no evidence to the contrary; it would have been prima facie obvious to one of ordinary skill in the art at the time of invention to use any nucleic acid comprising an unmethylated CpG motif (as long as it was not preceded by a C or followed by a G) regardless of origin (including bacterial DNA or eukaryotic DNA or sequences which do not hybridize to genomic DNA/RNA under high stringency conditions) with a reasonable expectation of success. The motivation to use any DNA comprising an unmethylated CpG motif not preceded by a C or followed by a G (including bacterial DNA and eukaryotic DNA and sequences which do not hybridize to genomic DNA/RNA under high stringency conditions) is provided by Krieg, which teaches, "(the) CpG dinucleotide in particular base contexts (is) the sole motif responsible for immune stimulation" (see p. 342, first paragraph).

Considering that Wooldridge teaches that administration of a oligonucleotide comprising an unmethylated CpG motif and monoclonal anti-CD20 antibody was effective for inhibiting

growth of a lymphoma in vivo, and also considering that there is no evidence to the contrary; it would have been prima facie obvious to one of skill in the art at the time of invention to use the method of Wooldridge to treat any type of B-cell lymphoma including B-CLL or marginal zone lymphoma. The motivation to use the treatment to treat any kind of lymphoma is provided by Wooldridge, which teaches, "Immunostimulatory oligodeoxynucleotides containing CpG motifs enhance the efficacy of monoclonal antibody therapy of lymphoma" (see p. 2994, title).

Considering that Wooldridge teaches a method of inhibiting the growth of a lymphoma by administering an oligonucleotide comprising an unmethylated CpG motif and an anti-CD20 antibody, and also considering that a number of anti-CD20 specific monoclonal antibodies were commercially available at the time of invention (as evidenced by Tables 1 and 2 of the specification; pp. 21-26 and p. 29), and considering there is no evidence to the contrary; it would have been prima facie obvious to one of ordinary skill in the art at the time of invention to use the method taught by Wooldridge using any anti-CD20 antibody (including the commercially available C2B8 or Rituximab monoclonal antibodies) in place of the specific anti-CD20 antibody taught by Wooldridge with a reasonable expectation of success. The motivation to use a commercially available anti-CD20 antibody would have been for convenience as commercially available monoclonal antibodies are easily obtainable.

Furthermore, considering that Wooldridge teaches that administration of the oligonucleotide and antibody are effective at reducing the growth of lymphoma tumors in mice when administered separately, and considering there is no evidence to the contrary; it would have been prima facie obvious to one of ordinary skill in the art at the time of invention to modify the treatment of Wooldridge such that the oligonucleotide and antibody were

administered together with a reasonable expectation of success. The motivation to do so is provided by Wooldridge, who teaches "immunostimulatory CpG ODN can enhance antibody dependent cellular cytotoxicity" (see p. 2998, abstract).

24. Claims 6 and 8-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Warren et al. (Clin. Lymphoma, June 2000; 1:57-61, IDS reference C159) in view of Krieg et al. (BioDrugs, 1998; 10:341-346.

Warren teaches a method of inhibiting B-cell lymphoma growth wherein a synthetic immunostimulatory oligonucleotide 20 nucleotides long comprising a phosphorothioate modified backbone and an unmethylated CpG motif (see p. 57, last paragraph and p. 58, first paragraph) and an anti-CD20 antibody are administered to mice having a B-cell lymphoma (see p. 58, second paragraph). Specifically, the tumor cells are 38C13 cells (p. 57, last paragraph). The treatment includes administration of the oligonucleotide and an anti-CD20 antibody wherein the oligonucleotide and antibody are administered together or separately (see p. 57, last paragraph; the same antibody used in Example 3 of the specification p. 76-77). Warren indicates that the concentration of oligonucleotide administered is in the range of 2-200ug, which would necessarily upregulate the expression of CD20 as mentioned above.

Warren does not specifically teach 1) the immunostimulatory nucleic acid is eukaryotic DNA; 2) the type B-cell lymphoma that is treated is a B-CLL or a marginal zone lymphoma; or 3) the CD20 antibody used is specifically C28B or Rituximab.

However, considering that Warren recognizes that bacterial DNA and synthetic DNA comprising unmethylated CpG motifs are effective immunostimulatory molecules (see p. 57,

abstract and first column), and also considering that the art recognizes that unmethylated CpG sequences (as long as it is not preceded by a C or followed by a G) can stimulate an immune response, regardless of the source of the nucleic acid (e.g. see Krieg p. 346 and 347, first paragraph) and also considering there is no evidence to the contrary; it would have been prima facie obvious to one of ordinary skill in the art at the time of invention to use any nucleic acid comprising an unmethylated CpG motif (as long as it was not preceded by a C or followed by a G) regardless of origin (including bacterial DNA or eukaryotic DNA or sequences which do not hybridize to genomic DNA/RNA under high stringency conditions) with a reasonable expectation of success. The motivation to use any DNA comprising an unmethylated CpG motif not preceded by a C or followed by a G (including bacterial DNA and eukaryotic DNA and sequences which do not hybridize to genomic DNA/RNA under high stringency conditions) is provided by Krieg, which teaches, "(the) CpG dinucleotide in particular base contexts (is) the sole motif responsible for immune stimulation" (see p. 342, first paragraph).

Considering that Warren teaches that administration of a oligonucleotide comprising an unmethylated CpG motif and monoclonal anti-CD20 antibody was effective for inhibiting growth of a lymphoma in vivo (as mentioned above), and also considering that there is no evidence to the contrary; it would have been prima facie obvious to one of skill in the art at the time of invention to use the method of Wooldridge to treat any type of B-cell lymphoma including B-CLL or marginal zone lymphoma. The motivation to use the treatment to treat any kind of lymphoma is provided by Warren, who teaches, "immunostimulatory CpG ODN enhance the efficacy of MoAb therapy, and multiple courses of combination therapy with CpG ODN can serve as an effective therapy for lymphoma" (see p. 57, abstract).

Considering that Warren teaches a method of inhibiting the growth of lymphoma by administering an oligonucleotide comprising an unmethylated CpG motif and an anti-CD20 antibody, and also considering that a number of anti-CD20 specific monoclonal antibodies were commercially available at the time of invention (as evidenced by Tables 1 and 2 of the specification; pp. 21-26 and p. 29), and considering there is no evidence to the contrary; it would have been prima facie obvious to one of ordinary skill in the art at the time of invention to use the method taught by Wooldridge using any anti-CD20 antibody (including the commercially available C2B8 or Rituximab monoclonal antibodies) in place of the specific anti-CD20 antibody taught by Warren with a reasonable expectation of success. The motivation to use a commercially available anti-CD20 antibody would have been for convenience as commercially available monoclonal antibodies are easily obtainable.

25. Claim 24 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wooldridge et al. (Blood, 1997; 89:2994-2998) in view of Goldenberg (WO 98/42378).

As mentioned above, the claim is very broad and encompasses the treatment of any type of cancer by administering: 1) any nucleic acid which induces the expression of any cancer antigen in any cancer cell; and 2) an anti-CD22 or anti-CD19 antibody.

Woolridge teaches a method for inhibiting the growth of a lymphoma tumor by administration of 300ug of a CpG ODN, (an amount sufficient to induce antigen expression of a number of cancer antigens; see p. 63 of the specification) and a monoclonal antibody (e.g., see p. 2996, Figure 4). Specifically, Woolridge teaches that the monoclonal antibody used in the method is and anti-CD20 antibody (e.g. see abstract).

Woolridge does not teach that the monoclonal antibody used in the method is an anti-CD22 antibody or an anti-CD19 antibody.

However, Goldenberg teaches a method for treating B-cell malignancies, including non-Hodgkin's lymphoma and chronic lymphocytic leukemia by administering an anti-CD22 antibody (e.g., see abstract; and p. 32, claim 1).

Therefore, it would have been prima facie obvious to one of skill in the art at the time of invention to substitute the anti-CD20 antibody of the Wooldridge method with the anti-CD22 antibody taught by Goldenberg, with a reasonable expectation of success for treating a lymphoma.

One of ordinary skill in the art would have been motivated to substitute the anti-CD22 antibody for the anti-CD20 antibody because Goldenberg teaches that anti-CD22 antibody therapy has been shown to be effective at treating lymphomas where CD20 antibody treatment failed to show a positive effect (see paragraph bridging p. 3-4); thus indicating that anti-CD22 antibody treatment may be superior to anti-CD20 antibody therapy.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is (703) 605-1165. The examiner can normally be reached on M-F (8:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

J. Eric Angell
December 29, 2002

DAVE T. NGUYEN
PRIMARY EXAMINER